LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report

Scientific discussion

Clopidogrel Genericon, 75 mg, film-coated tablet

(clopidogrel besylate)

SE/H/875/01/DC

This module reflects the scientific discussion for the approval of Clodogrel Genericon. Please note that the marketing authorisation was first approved with the name "Clopithan" and therefore this name is used throughout the document. The procedure was finalised at 2009-06-26. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Specifar S.A. has applied for a marketing authorisation for Clopithan, film-coated tablet, 75 mg claiming essential similarity to Plavix, film-coated tablet, 75 mg marketed in the EU (EU/1/98/069) by Sanofi Pharma Bristol Myers Squibb SNC. The product contains clopidogrel as active substance. For approved indications see the Summary of Product Characteristics. The reference product used in the bio-equivalence study is Plavix, film-coated tablet, 75 mg marketed by Sanofi Pharma Bristol Myers Squibb SNC in Germany.

II. QUALITY ASPECTS

II.1 Introduction

Clopithan is presented in the form of tablets containing 111.86 mg of clopidogrel besylate which corresponds to 75 mg of clopidogrel. The excipients in the tablet core are pregelatinised maize starch, microcrystalline cellulose, crospovidone, colloidal anhydrous silica and stearic acid. The film-coating consists of lactose monohydrate, hypromellose, titanium dioxide, triacetin, red iron oxide and carnauba wax. The tablets are packed in OPA/Aluminium/PVC/Aluminium blisters.

II.2 Drug Substance

Clopidogrel does not have a monograph in the Ph Eur.

Clopidogrel is a *white to almost white, crystalline powder* which is soluble in methanol and practical insoluble in water. The structure of clopidogrel has been adequately proven and its physico-chemical properties sufficiently described. The route of synthesis has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The active substance specification includes relevant tests and the limits for impurities/degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies under ICH conditions have been conducted and the data provided are sufficient to confirm the retest period.

II.3 Medicinal Product

Clopithan, film-coated tablet is formulated using excipients described in the current Ph Eur, except for titanium dioxide and iron oxide which are controlled according to Directive 95/45/EC. All raw materials used in the product has demonstrated compliance with Commission Directive 2003/63/EC and the NfG on Minimising the risk of transmitting Animal Spongiform Encephalopathy Agents via human and veterinary medicinal products (EMEA/410/01).

The product development has taken into consideration the physico-chemical characteristics of the active substance.

The manufacturing process has been sufficiently described and critical steps identified. Results from the process validation studies confirm that the process is under control and ensure both batch to batch reproducibility and compliance with the product specification.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies under ICH conditions have been performed and data presented support the shelf life claimed in the SPC, when stored below 30ºC.

III. NON-CLINICAL ASPECTS

III.1 Discussion on the non-clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to preclinical data, no further such data have been submitted or are considered necessary.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

A bioequivalence study with single doses of 75 mg clopidogrel was included in the application.

The study was a randomised, single dose, 4-way replicate crossover study. Subjects were assigned to one of the two sequences ABAB and BABA. Following an overnight fast, subjects were administered a 75 mg dose under fasting conditions with 240 ml of water. Subjects were kept fasting until 4 hours post dose. Blood samples were collected before dosing and up to 24 h hours after each administration. The study periods were separated by 7 day wash-out periods.

Clopidogrel in plasma was determined with a HPLC method with tandem mass spectrometry detection in house. Sample pre-treatment involved liquid-liquid extraction. Clopidogrel-D3 was used as internal standard (IS).

The statistical analysis was performed using the PROC MIXED in SAS on ln-transformed parameters.

Bioequivalence in AUC and C_{max} was demonstrated:

	AUC_{0-t}	**C_{max}**
Ratio (90% CI)	**101 (94-108)**	**93 (86-101)**

IV.2 Discussion on the clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to clinical efficacy/safety data, no further such data have been submitted or are considered necessary.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

User testing of the package leaflet has been performed and is acceptable.

The risk/benefit ratio is considered positive and Clopithan, 75 mg, film-coated tablet is recommended for approval.

VI. APPROVAL

The Decentralised procedure for Clopithan, film-coated tablet, 75 mg was successfully finalised on 26 June 2009.

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Public Assessment Report – Update

Scope	Procedure number	Product Information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached
						Y/N (version)

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